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Supporting Material

One-Pot, Catalytic, Asymmetric Syntheses of All Four Stereoisomers of a Dipropionate Synthon

General Methods. Quinidine was purchased from Acros Organics and used without purification. Trimethylsilylquinine was prepared from commercial quinine as previously reported.[1] Zinc powder was purchased from Fisher Scientific and activated by successive washes with concentrated HCl, deionized water, methanol and ether. 2-Bromopropionyl bromide was purchased from Aldrich Chemical Company and distilled under reduced pressure and stored in a sealed flask protected from light. Potassium triethylborohydride, zinc triflate, and sodium borohydride were purchased from Aldrich Chemical Company and used without purification. *N*,*O*-dimethylhydroxylamine was prepared from the hydrochloride salt by the literature procedure.[2] Tetrahydrofuran (THF) was purified by passage through activated alumina under N_2.[3] Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh).

General Procedure for Preparation of Optically Enriched Methyl Ketene Dimer. Zn powder (0.800 g, 12.5 mmol) was suspended in 3.5 mL of THF in a 50 mL distillation flask attached to a short path distillation apparatus and the pressure in the system was adjusted to 110 torr, whereupon the solvent began to mildly reflux. A solution of 2-bromopropionyl bromide (1.08 g, 5.00 mmol) in 3.5 mL of THF was added *via* a Teflon cannula over 5 to 8 min. Methylketene was collected as a THF solution in a 50 mL receiver flask cooled to 77K. After the addition of 2-bromopropionyl bromide was completed, the receiver flask was removed from the distillation apparatus, placed under N_2, and warmed to -78 °C to afford a lime green solution. This solution was added over 2 min *via* an insulated Teflon cannula to a solution of the catalyst (0.015 mmol) in 2.5 mL of THF. This solution was maintained 1.5 h at -78 °C to give a clear, colorless solution of the methyl ketene dimer of suitable purity for subsequent transformations.

General Procedure for the Preparation of Optically Enriched 1[3-Hydroxy-2-methylpentanoyl]azacyclopentane (1). To a solution of the methyl ketene dimer at -78 °C, prepared as above, was added 0.109 mL of pyrollidine (0.0932 g, 1.31 mmol) over 30 s. The appropriate reducing agent was then added immediately to this reaction mixture:

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[1] Calter, M. A. "Catalytic, Asymmetric Dimerization of Methylketene" *J. Org. Chem.* **1996**, *61*, 8006-8007.
[2] Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016-6023.
[3] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. S. *Organometallics* **1996**, *15*, 1518-1520.

Anti* Reduction.** Addition of 3.28 mL (3.28 mmol) of a 1.0 M solution of potassium triethylborohydride in ether to the β-ketoamide solution from above afforded a homogeneous reaction mixture, which was maintained at -78 °C for 0.5 h, and then quenched by the addition of 14 mL of a 1:1 MeOH:pH 7 buffer mixture. The mixture was warmed to 0 °C and 14 mL of a 1:1 MeOH:30% aqueous H_2O_2 mixture was added, and the heterogeneous mixture was stirred 0.5 h at 24 °C. This mixture was then extracted with CH_2Cl_2 (45 mL), the resulting aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. To the resulting oil was added one drop AcOH and 6 mL MeOH, and the mixture was residue was concentrated *in vacuo*. The addition and evaporation of MeOH and AcOH was repeated three times to yield a colorless oil. ^{1}H NMR analysis of the unpurified reaction mixture indicated that the *anti* **1**:*syn1** ratio was >95:5. Flash chromatography on silica gel (1 × 15 cm, step gradient from 50% to 80% EtOAc in hexanes, 5% steps) yielded 0.2222 g (48%) of *anti* **1** as a clear, colorless oil, the properties of which, except for optical rotation, exactly matched those reported previously for racemic *anti* **1**.[4] The rotation for (2*S*,3*S*) **1** was $[\alpha]_D$ 34° (*c* 1.02, $CHCl_3$). The rotation for (2*R*,3*R*) **1** was $[\alpha]_D$ -35.9° (*c* 1.035, $CHCl_3$).

Optical Purity Assay for *anti* 1. *Anti* **1** was converted into the corresponding hydroxy silylether by *tert*-butyldimethylsilylation of the secondary hydroxyl[5] followed by reduction of the amide to the primary alcohol.[6] The enantiomers of the hydroxy silylether were seperated by GC chromatography on a Chirasil-DEX CB column (25 m × 0.25 mm, df = 0.25 μm) at 110 °C with an average carrier gas velocity of 25 cm/s, retention time for the (2*R*,3*R*) hydroxy silylether = 31.42 min, retention time for the (2*S*,3*S*) hydroxy silylether = 31.75 min.

Syn* Reduction.** Addition of 0.5453 g (1.5 mmol) of $Zn(OTf)_2$ in 2.5 mL THF to the β-ketoamide solution from above afforded a homogeneous reaction mixture, which was maintained at -78 °C for 0.5 h. To this mixture was added 0.142 g (3.75 mmol) of sodium borohydride and the reaction mixture was maintained at -78 °C for 2h. The mixture was then raised to 0 °C, stirred for 15 min, and then quenched by the addition of 16 mL of a 1M aqueous HCl solution. The hetereogeneous mixture was warmed to 23 °C, stirred for 10 min at this temperature, and then extracted with 50 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. ^{1}H NMR analysis of the unpurified reaction mixture indicated that the *syn1**:*anti* **1** ratio was >95:5. Flash chromatography on silica gel (1 × 15 cm, step gradient from 40% to 50% EtOAc in hexanes, 2.5% steps) yielded 0.2050 g (47%) of *syn* **1** as a clear, colorless oil, the properties of which,

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4 Ireland, R. E.; Brown, F. R. *J. Org. Chem.* **1980**, *45*, 1868-1880.
5 Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.
6 Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1-12

except for optical rotation, exactly matched those reported previously for racemic *syn* **1**.[4] The rotation for (2*S*,3*R*) **1** was $[\alpha]_D$ 15.1° (*c* 1.01, $CHCl_3$). The rotation for (2*R*,3*S*) **1** was $[\alpha]_D$ -14.7° (*c* 1.015, $CHCl_3$).

Optical Purity Assay for *syn* 1. *Syn* **1** was converted into the corresponding hydroxy silylether by *tert*-butyldimethylsilylation of the secondary hydroxyl[5] followed by reduction of the amide to the primary alcohol.[6] The enantiomers of the hydroxy silylether were seperated by GC chromatography on a Chirasil-DEX CB column (25 m × 0.25 mm, df = 0.25 μm) at 150 °C with an average carrier gas velocity of 25 cm/s, retention time for the (2*S*,3*R*) hydroxy silylether = 30.97 min, retention time for the (2*R*,3*S*) hydroxy silylether = 33.99 min.

General Procedure for the Preparation of Optically Enriched 3-Hydroxy-2-methyl-*N*-methyl-*N*-methoxypentanamide (2). To a solution of the methyl ketene dimer at -78 °C, prepared as above, was added 0.100 mL of *N*,*O*-dimethylhydroxylamine (0.0839 g, 1.375 mmol) and 0.0065 g (0.069 mmol) of pyridone. The reaction mixture was warmed to 0 °C, maintained at this temperature for 4 h, and then recooled to -78 °C and the appropriate reduction agent was then added. The reduction conditions and reagents for the reduction were identical to those used to produce **1**. The analytical data for both enantiomers of *Syn* **2** matched those previously reported for these compounds.[7] The data for *Anti*-**2** follow; for (2*R*,3*R*) **2** , $[\alpha]_D$ -38.9° (*c* 1.025, $CHCl_3$), for (2*S*,3*S*) **2** , $[\alpha]_D$ 37.2° (*c* 1.04, $CHCl_3$); IR (thin film) ν 3445, 2970, 2940, 2880, 1640, 1460, 1390, 1180, 1120, 990; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.70 (s, 3 H,NOCH_3), 3.51-3.55 (m, 1 H, C_3H), 3.29 (d, 1 H, *J* = 7.6 Hz, O*H*), 3.18 (s, 3 H, NOCH_3), 2.90-2.97 (m, 1 H, C_2H), 1.42-1.55 (m, 2 H, CH_2), 1.21 (d, 1 H, *J* = 7.1, C(H)CH_3), 0.97 (t, 3 H, *J* = 7.4 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ 177.4, 75.4, 61.5, 39.6, 31.8, 28.2, 15.0, 10.2; Anal. Calcd for $C_8H_{17}N_1O_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 54.79; H, 9.81; N, 7.88.

Optical Purity Assay for *anti* 2. The enantiomers of ***anti* 2** were seperated by GC chromatography on a Chirasil-DEX CB column (25 m × 0.25 mm, df = 0.25 μm) with an average carrier gas velocity of 25 cm/s. The column was maintained at 100 °C for 25 min, and then temperature was raised at 1 °C/min for 20 min. The retention time for (2*R*,3*R*) **2** = 33.66 min, and the retention time for (2*S*,3*S*) **2** = 34.74 min. The diastereomers of **2** were also resolved under the same conditions.

Optical Purity Assay for *syn* 2. The enantiomers of ***syn* 2** were seperated by GC chromatography on a Chirasil-DEX CB column (25 m × 0.25 mm, df = 0.25 μm) with an average carrier gas velocity of 25 cm/s. The column was maintained at 100 °C for 25 min, and then temperature was raised at 1 °C/min for 20 min. The retention time for (2*R*,3*S*) **2** = 32.96 min, and

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[7] Cane, D. E.; Tan, W.; Ott, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 527-535.

the retention time for (2*S*,3*R*) **2** = 33.20 min. The diastereomers of **2** were also resolved under the same conditions.